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EDITORIAL

Adjuvant Therapy for Colon Cancer: Learning from the Past to Inform the Future

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Adjuvant treatment of colon cancer has been a clear success story over the last three decades. Since the seminal trial of Moertel demonstrating the efficacy of 5-fluorouracil (5-FU) with levamisole for stage III disease, to the current standard of care of oxaliplatin plus fluoropyrimidines delivered either as the FOLFOX or the XELOX regimen, a large number of randomized clinical trials have supported incremental advances in efficacy as well as modifications to retain efficacy while reducing toxicity and/or duration of therapy.[1–3] The Colon Clinical Trials Program of the National Surgical Adjuvant Breast and Bowel Project (NSABP) has been a fundamental cog in this wheel; many of the NSABP's trials have helped set or validate a standard of care. As such, it is useful to review the history of the NSABP's trial program, which Wilkinson et al. do in this issue.[4]

The pooled results of NSABP C-01 through C-05 reaffirm several facts. First, and most importantly, fluorouracil-based adjuvant therapy provides clear, clinically meaningful benefit to patients with stage III colon cancer. That this message warrants repeating is surprising, as it comes 20 years after the National Cancer Institute consensus statement.[5] However recent population-based data continue to demonstrate that, in the USA, up to 30% of the stage III colon cancer population is not treated with adjuvant therapy.[6] The reduced use of chemotherapy is particularly pronounced in the elderly, despite meta-analyses of randomized trials that demonstrated a similar benefit from chemotherapy in both young and older (age $\geq$70 years) patients.[6,7]

Second, the analysis confirms a more recent realization that the mechanism of benefit of 5-FU-based therapy is to dramatically reduce the recurrence rate in the first 2 years post surgery, which is when most recurrences occur. This short-term reduction in the recurrence risk translates into a durable survival benefit.[8] This phenomenon was confirmed in this NSABP analysis, where in the first year post surgery, chemotherapy reduced the risk of recurrence in stage III patients from 20% to 10% and from 21% to 15% in year 2. Following year 2, the recurrence risk was similar in chemotherapy-treated and control patients. This observation is critical for modern clinical trials, as it relates to both the optimal endpoint for a phase III adjuvant trial as well as the underlying biologic mechanism for benefit of a new therapy. Regarding the first point, for trials testing cytotoxic agents expected to have a similar antitumor effect to chemotherapy, this suggests that an early time point such as 2 or 3 years may be the most sensitive time point to identify a true biologic drug effect.[9,10] With regard to the underlying biologic mechanism of action of an adjuvant cytotoxic therapy such as 5-FU, it clearly reduces the risk of recurrent disease, as opposed to only delaying its occurrence. As such this therapy actually eradicates micrometastatic disease, a prerogative for a curative effect. A similar mechanism of action appears to be present for the addition of oxaliplatin to 5-FU; at 5- and 6-year follow-up in the more recent MOSAIC and NSABP C-07 trials the survival curves are continuing to separate and no increase in late recurrences has been observed.[11,12] However, in the recent NSABP C-08 trial which added the noncytotoxic, biologic agent bevacizumab to FOLFOX, only a short-term benefit in reduction of recurrence risk was observed, which disappeared after bevacizumab was halted, such that at 3-year follow-up the disease-free survival rates were almost identical in the two arms.[13] Thus, in trials of agents with noncytotoxic mechanism of action, short-term endpoints

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such as 2- or 3-year disease-free survival are likely inadequate to assess long-term survival benefits, as recurrences that are simply delayed as opposed to prevented will not result in long-term cure.

The report of Wilkinson et al. also provides data regarding the benefit of 5-FU-based adjuvant therapy in patients with stage II disease. Adjuvant therapy for patients with stage II disease has been a long-standing controversy, with primarily the NSABP advocating treatment and others finding very little benefit.[14,15] Fortunately, we now have randomized data from a large single clinical trial, the recent QUASAR study, where 5-FU-based chemotherapy was associated with significantly improved overall survival (OS) compared with surgery alone in largely stage II patients [5-year OS of 80.3% for chemotherapy versus 77.4% for observation; hazard ratio (HR) = 0.83, p = 0.02].[16] These data from a large single randomized trial provide stronger evidence and a more accurate estimate of the true benefit than that possible from the pooled analysis of trials presented by Wilkinson, in which no individual trial directly tested intravenous 5-FU-based therapy against surgery-alone control.[4] No amount of multivariate analysis can adjust for the potential for bias in such a comparison, particularly in one where the age distribution of the included patients clearly changed over time; protocols C-03 and C-04 excluded patients over the age of 71 years whereas such patients were allowed in C-01 and C-02, the former being the only two trials with no postsurgical treatment control arms.

The high rate of cure from surgery alone in patients with stage II disease dictates that any postoperative therapy given will be unnecessary for most patients who are cured by surgery alone. There is thus the critical need for prognostic and predictive markers to identify which patients are both at higher and very low risk of recurrence, and more importantly which patients may benefit from therapy. The NSABP authors' suggestion that "it is inconceivable that a future RCT studying adjuvant therapy for stage II and III colon cancer will ever include patients treated by surgery alone or even surgery followed by 5-FU/LV" is an overstatement given that such a phase III trial is ongoing within the US Intergroup at the present time (ECOG E5202), where patients with stage II colon cancer receive or do not receive adjuvant therapy depending on their status on 18q loss of heterozygosity (LOH) and microsatellite instability (MSI). Indeed, the promising data available for MSI to identify patients who are at very low recurrence risk and who do not appear to benefit from 5-FU support a no-treatment approach in MSI-H stage II colon cancer patients.[17–20] On the other hand, T4 N0 stage II colon cancers have a prognosis similar to (or even worse than) stage III cancers and should likely routinely receive adjuvant therapy. For the remaining intermediate-risk patients with stage II colon cancer, a signature of molecular makers might be able to further characterize patients with regard to their overall prognosis and whether or not they could benefit from a specific adjuvant treatment regimen.[17] Therefore, biospecimen resources to facilitate the identification and validation of prognostic and predictive markers, such as those available at the NSABP, will be critical for the future refinement of adjuvant treatment strategies in colon cancer.

Clinical trials continue to be the cornerstone of advancing medical practice, and nowhere is this more clear than in adjuvant colon cancer. The NSABP has and continues to conduct critical trials to advance our understanding, and the data from these trials continue to provide new insights many years after the primary questions are resolved.

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